Review article

Vulval intraepithelial neoplasia: clinical review

Nomenclature

Preinvasive neoplasia of the vulva has been recognised for over 75 years, but terminology to describe the disease has been confusing. Vulval carcinoma in situ (CIS) has been variously described as Bowen's disease, erythroplasia of Queyrat, carcinoma in situ simplex, Bowenoid papulosis, kraurosis vulvae, and leukoplakia. In 1983 the 3rd International Congress of the International Society for the Study of Vulval Disease (ISSVD) agreed a modified nomenclature for the uniform classification of vulval intraepithelial neoplasia (VIN). This classification grades vulval atypia in a manner similar to that commonly used for intraepithelial neoplasia of the cervix. VIN is thus classified as: (1) squamous (with or without evidence of infection with human papillomavirus (HPV)); (a) VIN I (showing mild atypia); (b) VIN II (moderate atypia); (c) VIN III (severe atypia, CIS); or (2) non-squamous (a) Paget's disease; (b) melanoma in situ (showing atypical melanotic hyperplasia). The following discussion deals only with squamous cell VIN.

Clinical profile

VIN has been considered previously to be an uncommon disease afflicting postmenopausal women in their seventh and eighth decades. Though the incidence of VIN is unknown, the number of diagnosed cases has greatly increased since 1970, which reflects both an increased awareness of the disease and a real increase in incidence. During that period, the mean age of diagnosis of VIN III fell from over 50 to under 38. In this clinic the modal or most common age of diagnosis of VIN III is 30, though some patients have been in their teens; 40% of women with VIN III were nulliparous. An association between VIN and sexually transmitted infection has been established in 20-60% of patients with VIN, and a tendency to increasing incidence was shown in later studies. Gonorrhoea has been diagnosed in up to one third of women with VIN III, and this no doubt contributes to the high incidence of nulliparity.

An association between VIN, particularly VIN III, and other genital tract neoplasia is common. Of patients with VIN III, 30% have synchronous or metachronous neoplasia, including invasive cancer, at another genital site. More specifically, at least 20% of women with VIN III have associated cervical intraepithelial neoplasia (CIN) III. This proclivity to multicentric disease is important in view of the increasing incidence of VIN in younger women, and it influences management.

Aetiology

The aetiology of VIN is unknown, but its increasing incidence in young women, its multifocal distribution, and its association with other lower genital tract neoplasia suggest a possible viral origin. The increased incidence of VIN parallels the increase of genital infection with herpes simplex virus (HSV) and human papillomavirus (HPV) in recent decades.
Recent research has shown an association between infection with HSV 2 and VIN III. Kaufman et al reported the presence of non-structural proteins induced by HSV 2, as well as serum IgG antibodies against HSV 2, in nine of 10 VIN III lesions. Cabral et al also showed non-structural HSV 2 protein in biopsy specimens from vulval neoplasia lesions, but attempts to culture the virus or to show viral particles by electron microscopy were unsuccessful.

An increasing volume of research implicates specific sexually transmitted types of HPV in vulval neoplasia. Charlewood and Shippel first described the malignant transformation of vulval condylomata acuminata in the South African Bantu in 1953. Since then the clinical association between vulval HPV infection and neoplasia has been established. Friedrich reported a history of condylomata acuminata in one third of cases of VIN III. In this clinic, a history of condylomata acuminata is obtained in 25% of cases of VIN III, and associated subclinical HPV infection is present in over 70% of cases. Common histological evidence of HPV infection in biopsy specimens from VIN III lesions further shows the association between the HPV infection and VIN. Molecular hybridisation studies undertaken in this clinic have shown HPV 16 deoxyribonucleic acid (DNA) in over 70% of biopsy specimens from VIN III lesions and in over half of those from vulval carcinomas. The viral genome is episomal in the pre-invasive biopsy specimens but is often integrated into the host genome in malignant tissue, which suggests that the association is more than casual. HPV 16 is strongly implicated in cervical carcinogenesis, and the strong association between vulval and cervical neoplasia suggests a possible common aetiology, primarily a field effect of specific sexually transmitted...
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Types of HPV.

Natural history

A continuum from preinvasive to invasive vulval neoplasia has not been clearly established, and the malignant potential of VIN remains uncertain. Earlier reports of progression of carcinoma in situ to invasive cancer led many workers to regard VIN as being a preinvasive cancer rather than a premalignant condition. This justified an extensive surgical approach to treatment. Follow up of untreated cases, however, indicated that the disease is as likely to regress as to progress. In younger women particularly VIN tends to be multifocal, and the risk of progression is considered to be low, probably less than 5%. Similarly, the time of transition from VIN III to invasive carcinoma seems to be long because of the 20 to 30 year difference between the average age of women with VIN III and those with vulvar cancer. In older women VIN tends to be unifocal, and the malignant potential appears to be greater. Similarly, immunosuppressed women seem to be at greater risk of the rapid advance of preinvasive disease.

Though the malignant potential of VIN appears to be low, progression of VIN III to invasive cancer does occur. Karyotypic analysis of biopsy specimens from VIN III lesions shows aneuploid DNA content in most, which suggests a malignant potential. Abnormal mitotic figures are often seen on histological examination. The intraepithelial stages may persist for long periods and progress slowly in the early stages, but may accelerate rapidly, particularly after the basement membrane has been penetrated. This apparent malignant potential of VIN and the risk of associated neoplasia, particularly of the cervix, underlie the need for accurate diagnosis and conservative but vigilant management.

Diagnosis

In the absence of a sensitive screening test for detecting VIN, the diagnosis depends on an awareness of symptomatology, familiarity with clinical and colposcopic appearances, and the liberal taking of (preferably colposcopically directed) biopsy specimens. The value of careful inspection of the vulva during gynaecological examination cannot be overstated, and inspection is the most productive diagnostic technique. The magnified illumination of the colposcope improves the accuracy of diagnosis, particularly of multifocal lesions, and permits examination of the lower genital tract (including the cervix, vagina, and perianal regions) to exclude multicentric disease.

At least half the patients with VIN are symptomatic. Vulval pruritis, burning, and pain are the most common symptoms. Patients may present with a vulval lump or with recurrent condylomata acuminata. The presence of a distinct mass, bleeding, ulceration, or a discharge strongly suggest invasive disease.

The clinical appearance of VIN is variable. VIN III lesions may be papular or macular, single or multiple, discrete or coalescent. Over 60% of lesions on the cutaneous surface of the vulva are white, lichenified, or hyperkeratotic plaques, and are often diagnosed as "leukoplakia". Lesions of the mucous membrane usually look like erythematous macules. About 15% of VIN III lesions are hyperpigmented and are thus readily diagnosed clinically. These lesions are described as bowenoid papulosis by some authors, but are more appropriately designated VIN, usually VIN III.

Parakeratosis is a common feature of VIN III. This is retention of nuclear chromatin material in the usually acellular keratin layer of the epithelium, and is thus a marker of abnormal maturation. It is identifiable using the Collins toluidine blue test. A 1% aqueous solution of toluidine blue, a nuclear stain that will fix to superficial nuclei, is applied to the vulva and left to dry for two to three minutes. The area is then decolourised with a solution of 1% acetic acid. Areas of parakeratosis and suspicious foci of increased nuclear atypia retain the dye and acquire a deep blue tinge, whereas normal skin accepts little or none of the dye. Unfortunately, hyperkeratotic lesions, though often neoplastic, stain poorly, whereas benign excoriations and fissures often look brilliant. There are therefore high rates of false positive and false negative results. Colposcopy has therefore emerged as being a more accurate diagnostic technique, and toluidine blue should not be applied until a thorough colposcopy examination has been performed.

The addition of 5% acetic acid to the vulval skin will produce prominent blanching of non-pigmented VIN lesions after three to five minutes. This "acetowhite" epithelium is then best assessed using the colposcope, which permits accurate mapping and biopsy of atypical vulval skin. In the presence of extensive multifocal or multicentric disease, this examination is best performed under general anaesthetic to permit thorough examination of the lower genital tract. Biopsy specimens may often be taken under local anaesthetic, however, which causes patients minimal discomfort. Adequate biopsy specimens are obtainable using an "alligator jaws" instrument, such as the Patterson rectal biopsy forceps, which permit adequate traction of the skin and sampling of deeper layers of epithelium. Contiguous structures, such as the clitoris, urethral meatus, lower vagina, and perianal region, must be carefully examined.
Lesions characterised colposcopically by bizarre dilated epithelial capillaries or friable yellowish epithelium must be regarded with suspicion, and should be evaluated by wide local excision to exclude invasive disease. Indurated, nodular, or ulcerated lesions should also be excised. VIN superimposed on longstanding condylomata acuminata or chronic dermatological conditions, particularly in elderly or immunosuppressed women, must also be managed with extreme caution.

The high incidence of associated, often silent, sexually transmitted disease in women with VIN demands thorough examination and investigation to exclude infection with HPV, HSV, *Chlamydia trachomatis*, or *Neisseria gonorrhoeae*. Serological screening for syphilis should be performed in each case.

**Treatment**

Though the original treatment advocated for vulval carcinoma in situ was wide local excision, in the 1960s...
simple vulvectomy became the standard management. Recently, however, the trend has been to more conservative treatment in managing VIN. The risk of progression of VIN to invasive cancer is considered to be lower than previously assessed, and the rate of progression is generally slow. Virally induced inflammatory atypia may produce bizarre cellular morphology that simulates neoplasms, and epithelial atypia induced by infection with HPV may be diagnosed as VIN. The increasing evidence implicating specific HPV types in the aetiology of vulval neoplasia has led to the consideration of regression of disease in immunocompetent individuals. Spontaneous regression does occur, particularly in pregnancy. VIN is found increasingly in younger women, and the physical and psychological sequelae of radical treatment have therefore become less acceptable. Indeed, a period of observation alone without treatment may be justified for VIN in selected patients who are reliably followed up, particularly if they are pregnant or temporarily immunosuppressed. In this clinic, however, two women, both under 40, developed early invasive carcinoma during observation periods of less than two years.

The three preferred treatments of VIN are wide local excision, skinning vulvectomy with split thickness skin graft, and carbon dioxide laser vaporisation. Most localised VIN lesions are managed very effectively by wide local excision, allowing a border free of disease of at least 5 mm, with primary approximation of the defect. Healing is usually uncomplicated, and the outcome is cosmetically and functionally good. The elasticity of the vulval skin and mucus membranes permits the preservation of sexual and reproductive functions, which is particularly important in young patients. Excision of VIN permits careful histological examination to exclude early invasive disease and to ensure clear margins of excision. If the margins are not free of disease, the rate of recurrent disease is over 50%. Wide local excision with adequate disease free margins achieves a 90% cure rate for localised VIN.

The skinning vulvectomy and skin graft procedure was introduced by Rutledge and Sinclair, and is particularly useful for managing extensive multifocal VIN, particularly if the hair-bearing areas are affected. Lesions are carefully mapped, and a shallow layer of vulval skin is excised while the subcutaneous tissue of the vulva is preserved. The vulval skin at risk is replaced with epidermis from a donor site on the thigh or buttock. The clitoris is always preserved, any lesions on the glans being superficially excised. The epithelium regenerates without loss of sensation. DiSaia and Rich reported a 39% recurrence rate in 39 patients with VIN III treated by skinning vulvectomy followed by split thickness skin graft. No recurrences occurred in the grafted areas, however, but in perianal, presacral, and periclitoral areas that had been preserved for functional or cosmetic reasons.

The carbon dioxide laser has become widely used in managing VIN during the past decade, as it provides effective and non-multilating treatment. Laser vaporisation must be preceded by thorough and expert preoperative and intraoperative colposcopy of the vulva, periclitoral, perianal, and vaginal areas as well as the cervix. All suspicious areas must be biopsied and, if invasive disease cannot be excluded colposcopically, then definitive histology of a widely excised lesion must be obtained. If invasive disease is excluded, the carbon dioxide laser permits destruction of the entire area of abnormal epithelium to a shallow but adequate depth, which permits rapid healing from keratinocytes in underlying pilosebaceous glands. A cosmetically pleasing result is obtained, irrespective of the area ablated, provided that destruction does not extend beyond the mid dermis. Extensive disease affecting both hair-bearing areas and mucus membranes may be treated best by combining excision of lateral lesions and primary approximation or skin graft with carbon dioxide laser ablation of the inner lesions. Of 50 patients with VIN III treated by carbon dioxide laser vaporisation in this clinic, six have returned with recurrent disease, which gives a cure rate of 88%. Townsend et al reported a 94% cure rate in 33 patients treated by carbon dioxide laser. Baggish and Dorsey reported 31 (89%) of 35 patients cured of disease.

The treatment of VIN has become more conservative to preserve sexual and reproductive function and to prevent the adverse sequelae of more radical vulval surgery. Patients must be reassessed at regular intervals for life, and attention must be paid to the cervix and the entire lower genital tract extending into the perianal, anal, and presacral regions. Recurrence of VIN does not carry the ominous implication of recurrence of cancer and thus, if diagnosed, can be managed again readily using conservative treatment.

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References


